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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/460,216	12/13/1999	GRAHAM P. ALLAWAY	50875-F-PCT-	2202

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EXAMINER	
PARKIN, JEFFREY S	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/460,216	ALLAWAY, G. P. ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

~~1)☒ Notice of References Cited (PTO-892)~~

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

Detailed Office Action

37 C.F.R. § 1.114

A request for continued examination under 37 C.F.R. § 1.114, including the fee set forth in 37 C.F.R. § 1.17(e), was filed 05 January, 2004, in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114. Applicants' submission filed on 29 August, 2003, has been entered. Claim 61 is currently under examination.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 61 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). The claim has been amended to introduce a new limitation vis-a-vis the binding specificity of the non-peptidyl agent. The claim now specifies that the agent of interest is capable of binding to the CCR5 chemokine receptor, but **not** the CXCR4 chemokine receptor. Perusal of the disclosure failed to provide support for the claimed limitation.

Claim 61 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). *In re Rochester*, 358 F.3d 916, 69 U.S.P.Q.2d 1886 (C.A.F.C. 2004).

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc., v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116. The issue raised in this application is whether the original application provides adequate support for the broadly claimed genus of **non-peptidyl agents** that are capable of abrogating HIV-1 infection by binding to the CCR5 chemokine receptor. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the biomolecule of interest. *In re Bell*, 991 F.2d 781, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993). *In re Deuel*, 51 F.3d 1552, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995). A

lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 U.S.P.Q.2d 1895, 1905 (Fed. Cir. 1995). The court noted in this decision that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not reasonably lead those skilled in the art to any particular species.

An applicant may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. For some biomolecules, examples of identifying characteristics include a nucleotide or amino acid sequence, chemical structure, binding affinity, binding specificity, and molecular weight. The written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. Without such a correlation, the capability to recognize or understand the structure form the mere recitation of function and minimal structure is highly unlikely. In the latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement. *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43 U.S.P.Q.2d 1398, 1404, 1406 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998). *In re Wilder*, 736 F.2d 1516, 1521, 222 U.S.P.Q. 369, 372-3 (Fed. Cir. 1984). Factors to be considered in determining whether there is

sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

The claim of the instant application is broadly directed toward **any non-peptidyl agent** that is capable of abrogating HIV-1 infection through CCR5 binding interactions. The disclosure provides an *in vitro* resonance energy transfer (RET) screening assay that enables the skilled artisan to detect HIV-1 fusion events. However, the disclosure fails to provide any structural guidance pertaining to suitable non-peptidyl compounds that can reasonably be expected to function in the claimed methodology. The only non-peptidyl compound described in the specification is specific for CXCR4, not CCR5. The disclosure fails to identify suitable chemical compounds with the desired activity. The disclosure fails to provide any guidance pertaining to the three-dimensional configuration of the CCR5 receptor. Thus, the skilled artisan can not employ a rational drug-screening strategy. Basically, applicants have provided a generic screening method and invited the skilled artisan to figure out which non-peptidyl compounds may be reasonably expected to function in the recited manner. This clearly fails to meet the requirements set forth under this statute.

Claim 61 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claim is broadly directed toward a method for inhibiting HIV-1 infection of $CD4^+$ cells through the administration of a non-peptidyl inhibitory agent that is capable of binding to the CCR5 chemokine coreceptor.

As previously set forth, the legal considerations that govern enablement determinations pertaining to undue experimentation are

disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide any guidance pertaining to the structural requirements of any given non-peptidyl inhibitor. The disclosure fails to teach which **chemical structures** are critical for binding to any given chemokine coreceptor and which structures are critical for the antiviral activity. The disclosure fails to identify any parent compounds, or derivatives thereof, that can reasonably be expected to function in the desired manner. Thus, the skilled artisan has been extended an undue invitation to further experimentation to try to identify putative antiviral agents and determine their structures.

2) The disclosure fails to provide sufficient guidance pertaining to the three-dimensional structure of CCR5 or the molecular determinants modulating HIV-1 envelope/coreceptor/antiviral binding interactions. In order to rationally design a putative therapeutic, the skilled artisan would need a knowledge of those portions of CCR5 or CXCR4 that should be targets of any given antiviral. However, the specification is silent pertaining to this concern and fails to identify any critical regions of the chemokine coreceptors that should be the targets of antiviral development.

3) The disclosure fails to provide any working embodiments the meet the claimed limitations. While it is noted that the disclosure describes the identification of a putative antiviral agent (e.g., JM3100), nevertheless, this compound is a bycyclam agent that is

directed toward CXCR4, not CCR5. There are no other examples involving non-peptidyl agents provided in the disclosure.

4) The claims are of excessive breadth and encompass any given putative antiviral agent without providing any meaningful structural limitations concerning that agent. The disclosure simply fails to support such breadth in the claim language.

5) The prior art describes a number of concerns pertaining to the development of antivirals, particularly fusion inhibitors. First, it is well-known that the chemokine family includes a large number of proteins that share limited genetic relatedness (~ 20%) (Proudfoot *et al.*, 1999; Proudfoot *et al.*, 2000). Thus, it appears unlikely that any given inhibitor will have a broad range of activity, particularly in the absence of the identification of any critical molecular determinants that are shared by all members of the family. Second, even if a putative antiviral compound was identified, there are a number of important immunological of therapeutic concerns that need to be considered (Berger *et al.*, 1999). For instance, will the loss of normal chemokine receptor function of a specific coreceptor be tolerated and accepted in the host? Will the impairment of CCR5 coreceptor usage accelerate disease progression by enhancing the selection for CXCR4 coreceptor usage? Do multiple members of the coreceptor repertoire need to be blocked in order to achieve a therapeutic effect? The disclosure is silent pertaining to these concerns.

Moreover, it has been well-established that the development of suitable HIV-1 therapeutics has been a long and arduous process, often ending in failure (Öberg and Vrang, 1990; Yarchoan and Broder, 1992; Gait and Karn, 1995; Flexner and Hendrix, 1997). This is due to a number of considerations such as a failure to understand the molecular determinants modulating many viral protein and host cell factor interactions, the failure of *in vitro* tissue culture studies and *in vivo* animal models to adequately predict clinical efficacy, the failure of many compounds to have acceptable pharmacological profiles, despite initial favorable *in vitro* and *in vivo* activities, and the failure of related structural analogs to

function in the desired manner, which provides further evidence of the specificity of these molecular interactions. The difficulties associated with developing efficacious anti-HIV-1 agents are best summarized by Gait and Karn (1995) who state (see Conclusions, p. 37):

> There can be few tasks in biotechnology that are more challenging than designing antiviral drugs. All of the protease inhibitors that have entered into clinical trials are potent inhibitors of HIV-1 replication in cell culture, and exhibit remarkable selectivities for the viral enzyme. Unfortunately, early protease inhibitors tended to suffer from problems of **short serum half-life, poor availability and rapid clearance.** As these pharmacokinetic problems have been addressed and solved, **new difficulties have emerged from the resultant clinical experience, such as sequestration of the drug by serum proteins, drug resistance and uneven distribution throughout the body.** Since these types of problems are **unpredictable,** it remains necessary to take into account the pharmacological parameters in any drug development programme at the earliest possible stage.

The disclosure fails to provide any guidance pertaining to these caveats. Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Applicants provide a detailed traversal and submit that the invention is fully enabled. It was argued that the disclosure provides an RET assay that can be utilized to screen for suitable compounds. Reference was made to a second declaration by Dr. Dragic. Dr. Dragic also asserted that the specification provides a generic RET screening method which can be utilized to identify compounds with the desired properties. This declaration did not provide any data demonstrating that applicants had identified such compounds at the time of filing. Exhibits were also provided in support. However, the majority of these exhibits were published well after the filing data of the claims.

Applicants are reminded that in order to overcome a *prima facie* case for lack of enablement, applicants must demonstrate that the disclosure was enabled as of the filing of the application (see

M.P.E.P. § 2164.05(a)). Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. *In re Gunn*, 537 F.wd 1123, 1128, 190 U.S.P.Q. 402, 405-06 (C.C.P.A. 1976). *In re Budnick*, 537 F.2d 535, 538, 190 U.S.P.Q. 422, 424 (C.C.P.A. 1976). Thus, the observation that others have come up with a small number of compounds well after the filing date of the instant application, would not lead the skilled artisan to conclude that the invention was enabled at the time of filing.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 9:30 AM to 7:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, Laurie Scheiner or James Housel, can be reached at (571) 272-0910 or (571) 272-0902, respectively. Direct general inquiries to the Technology Center 1600 receptionist at (571) 272-1600.

Formal communications may be submitted through the official facsimile number which is (703) 872-9306. Hand-carried formal communications should be directed toward the customer window located in Crystal Plaza Two, 2011 South Clark Place, Arlington, VA. Applicants are directed toward the O.G. Notice for further guidance. 1280 O.G. 681. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

16 April, 2004